REMARKS

Rejection of the claims under 35 USC § 102:

Claims 1, 4-6, 10, 13, and 14 have been rejected under 35 U.S.C. 102(e) as being unpatentable over Fosnaugh et al. (U.S. 2003/0143732) as evidenced by Thierry et al. (US 6,110,490).

The Action argues Fosnaugh teaches a) that RNA can be modified b) the modification can be labile and that c) RNA can be delivered using a liposome vehicle. Therefore, according to the Action, Fosnaugh teaches labile linkage of a hydrophobic group to an siRNA and specific use of this modified siRNA with transfection reagents.

The Action also argues that the term "enhance" is interpreted to mean any interaction of a siRNA molecule comprising a hydrophobic group with a transfection reagent such that the siRNA is capable of entering a cell. It is the Applicants' opinion that this interpretation is excessively broad and expands the definition beyond the ordinary and customary meaning both in the field and in the context of Applicants' disclosure. The term "enhance" is defined by Merriam-Webster Dictionary as "heighten or increase". Therefore, the interpretation of "enhance" to encompass any interaction is incorrect. Further, the claim states that association of the reversibly modified RNA with the transfection reagent is enhanced via hydrophobic interactions. The term enhance specifically connects interaction and association of the reversibly modified RNA with the transfection reagent. Inherent in the term enhance, by virtue of its definition, is that the interaction is increased relative to the RNA not having the hydrophobic modification.

20030143732 July 31, 2003

As stated in the abstract, and at paragraph [0002], '732 teaches, "Specifically, the invention relates to short interfering nucleic acid molecules (siRNA) capable of mediating RNA interference (RNAi) against adenosine A1 receptor (ADORA1) gene expression." In disclosing siRNA molecules capable of inhibiting the ADORA1 gene, the inventors of '732 go on to present a laundry list of siRNA modifications, delivery vehicles, and delivery routes that are known in the art to be possible.

'732 teaches that siRNA can be modified and that the modification may be to a ribose, a nucleotide base, or to a phosphate backbone linkage [0026, 0167]. '732 specifically lists more than 150 modifications [0018, 0024, 0034, 0037, 0040, 0050, 0061, 0068, 0067, 0068, 0109, 0168, 0171, 0172, 0181, 0182, 0187, 0191] and repeatedly states that the specifically recited modifications are non-limiting examples and that *any other* nucleotide base modification is encompassed. Thus, the publication provides merely a laundry list of siRNA modifications which are known or theoretically possible. While '732 further states that each of these modifications should not affect interaction of siRNA with a target RNA and/or other factors [0103], the authors provide no teaching as to which modifications will or will not affect this interaction.

'732 further teaches that the modifications, including conjugates, may be used to: increase resistance to nuclease degradation, improve cellular uptake, improve stability of the interaction with the target, improve stability of the interaction with itself, enhance affinity and specificity to nucleic acid targets, overcome potential limitations of in vivo stability and bioavailability, provide longer half-life in serum, target particular cells or tissues, module polymerase activity, improve RNAi activity against ADORA1, enhance helical thermal stability, enhance shelf life, enhance half-life in vitro, enhance stability, or ease introduction to target site [0026, 0034, 0035, 0068, 0097, 0099, 0101, 0104, 0109, 0170, 0171, 0192]. Each of these is merely a desired effect. '732 does not teach which modifications may be used to affect which activities, properties, or characteristics. Further, '732 does not teach that the modification may be used to enhance interaction with a transfection reagent. More specifically, '732 does not teach a hydrophobic modification to enhance interaction with an amphipathic transfection reagent.

'732 teaches that conjugates and complexes can be used for delivery of biologically active molecules, (small molecules, lipids, phospholipids, nucleosides, nucleotides, nucleic acids, antibodies, toxins, negatively charged polymers, peptides, hormones, carbohydrates, polyethylene glycols, polyamines, proteins, and other polymers) across membranes [0172]. '732 does not teach or suggest which conjugate molecules or complexes can be used for delivery of which biologically active molecules across membranes or whether all of the conjugates and

complexes are suitable with all of the biologically active molecules. '732 also does not teach how to *make* any complexes.

'732 teaches that transporters (e.g. conjugates) used to transport molecules across membranes may be used individually or as part of a multi-component system, may be used with or without degradable linkers, and may or may no be linked to the biologically active molecule by a biodegradable linker [0172]. '732 does not teach or suggest *which* transporters should be used individually or as part of a multi-component system, *which* transporters may be used with degradable linkers, *which* transporters should be used without degradable linkers, or *which* transporter should be linked to the biologically active molecule and *which* can not. Nor does '732 teach under which circumstance or conditions each of these unspecified transporters should or should not be part of a multi-component system, contain a biological linker or be linked to a biologically active molecule. Further, '732 does not teach any specific use for a biodegradable linkage, merely that such linkages may be used in the nucleic acid backbone, nucleic acid sugar, or nucleic acid base modifications [0173].

'732 teaches that conjugates and/or complexes of siRNA molecules may be used to facilitate delivery, transfer therapeutic compounds across cellular membranes, alter pharmacokinetics, or alter module localization [0172]. '732 does not teach which conjugates or complexes are suitable for each of these desired outcomes.

'732 teaches that the siRNA can be added directly to, complexed with, or mixed with: cationic lipids, liposomes, surface-modified liposomes, pH sensitive liposomes, pharmaceutically acceptable formulations, immunoliposomes, carriers, diluents, hydrogels, cyclodextrins, nanoparticles, biodegradable nanocapsules, microshperes, bioadhesive microspheres, proteinaceous vectors, fusogenic peptides, stabilizer, buffer, biopolymers, biodegradable polymers, troches, lozenges, aqueous suspensions, oily suspensions, dispersible powders or granules, emulsion, syrups, elixirs, *other* delivery vehicles, or otherwise delivered to target cells or tissues [0124, 0193, 0194, 0195, 0199, 0200, 0203]. '732 teaches that these vehicles may be used for storage or administration [0201]. '732 provides no teaching or direction for choosing a particular vehicle or choosing any modification in combination with any particular vehicle.

'732 teaches the used of liposome for delivery of the siRNA. At [0195] '732 states, "When it is desired to use a liposome delivery mechanism, *standard protocols* for formation of liposomes can be followed." While liposomes are amphipathic transfection reagents as instantly claimed, it is *not* standard in the art to modify a nucleic acid to add a hydrophobic group prior to formation of the liposome/nucleic acid complex.

'732 contains an astonishing range of modifications and delivery vehicles which may potentially be used to delivery their siRNA. '732 also teaches a wide range of desired properties for these modifications and delivery vehicles. However, there is no data of any kind to support any particular modification or combination of modification and delivery vehicle. The authors provide no clear guidance as to which modifications, delivery vehicles, or combinations possess the desired properties. The skilled person would consider it totally far fetched any modification could be used in relation to any of the delivery vehicles or that any of the modifications would possess all the desired properties.

The operative principle of Applicants' invention, labile linkage or a hydrophobic group to the siRNA and then use of the hydrophobic group to enhance interaction with a transfection reagent is neither understood or taught by '732 so as to be intelligently reproduced. "A prior use, in order to negative novelty, must be something more than an accidental or casual one. It must, indeed, be so far understood and practiced, or persisted in, as to contribute to the sum of human knowledge and be accessible to the public, becoming an established fact in the art." (Anthracite Separator Co. v. Pollock). For one skilled in the art to combine separately disclosed parts taught by '732 would be "purely a matter of chance and not the inevitable result of its process." (International Nickel Co. v. Ford Motor Co.) and therefore not an anticipation.

It is the Applicants' opinion that '732 patent is not enabling and fails to describe the Applicants' instant invention sufficiently to enable a person of ordinary skill in the art to carry out Applicants' invention. There is no specific teaching in the '732 that would lead to Applicants' invention. One skilled in the art, on reading '732, would have no understanding as to which modifications, alone or in some further unknown combination, would have any particular desired

characteristic. Except for an siRNA for inhibiting the adenosine A1 receptor (ADORA1) gene expression, the art of siRNA delivery is not advanced by the teaching of '732.

The Action correctly notes that the Examiner previously stated that the claims and specification "fail to provide adequate written description of the infinite number of hydrophobic groups that enhance the interaction of the claimed RNA with a transfection reagent." Applicants have amended the claim to recite a hydrophobic group containing 1 to 20 carbon atoms. Support for the limitation can be found in the specification in Figures 1 and 2 and in examples 1-4: an acetyl group adds a hydrophobic group having 1 carbon atom, a trimethyl silane (TMS) group adds a hydrophobic group having 3 carbon atoms, an lauroyl group adds a hydrophobic group having 11 carbon atoms, and a dimethyloctadecylsilane group adds a hydrophobic group having 20 carbon atoms.

Claim 5 has been amended to recite the labile bond is a silyl ether or a maleamate. Support for a silyl either can be found in the specification at page 2 lines 1-3. Support for a maleamate can be found at page 8 line 17 to page 9 line 8. While the term maleamate is not specifically used in the specification, reaction of a maleic anhydride with an amine, as described, is known in the art to yield a maleamate bond.

Claims 1, 4-6, 10, 13, and 14 have been rejected under 35 U.S.C. 102(e) as being unpatentable over Lewis et al. (U.S. 2003/0143204) as evidenced by Thierry et al. (US 6,110,490). Applicants have filed a declaration under 37 CFR 1.132 to overcome the rejection. The labile attachment of a lipid to a biologically active compound, as claimed in the instant invention and as disclosed in '204, was invented by Sean Monahan and Jon Wolff. Therefore, the disclose of '204 relied upon for the rejection is not by another. Applicants request reconsideration of the rejection.

Rejection of the claims under 35 USC § 103:

Claims 1, 4-6, 10, 13, and 14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Fosnaugh et al. (U.S. 2003/0143732) or Lewis et al. (US 20030143201), taken with Manoharan, M. (Biochimica et Biophysica Acta 1489, 1999: 117-130) and Goldsborough (WO

01/94626). It is the Applicants' opinion that the amendments and arguments made above in response to the 102 rejections are sufficient to overcome the 103 rejections.

The Examiner's rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendment and arguments, it is submitted that claims 1, 4-6, 10, 13, and 14 should be allowable.

Respectfully submitted,

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I hereby certify that this correspondence is being transmitted to the USPTO on this date: 11 May 2010 .

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